Stakeholder's Technical Meeting Report: Epidemiology and control options of respiratory syncytial virus (RSV) in the Kenyan context

Executive summary

The RSV stakeholders' meeting was an initiative of KEMRI Centre for Global Health Research (CGHR) and CDC-Kenya and KEMRI-Wellcome Trust who are involved in conducting RSV research in Kenya. They felt that there was need to start early engagement with the Country's experts from policy makers, pediatricians, academia to researchers and to create awareness of the country's RSV disease burden, vaccine development, potential implementation strategies and ongoing research.

RSV is now recognized as the major cause of severe pneumonia among infants especially those below 6 months of age, worldwide. This has been due to reduction of pneumonia previously attributed to bacterial infections through introduction of *Haemophillus influenzae* type b (Hib) and pneumococcal conjugate (PCV10) vaccines. Different vaccine options for preventing RSV disease among infants are in advanced stages of development and may get licensure soon. The meeting was therefore meant to create a platform for discussion on the country's preparedness and way forward on the prospects of taking up new interventions.

The meeting was held at KEMRI Headquarters Conference Hall in Nairobi on 17th September 2018 from 10 am to 2.00 pm. It was organized by the KEMRI Deputy Director Research and Development and jointly facilitated by researchers from KEMRI-Wellcome Trust, CDC-Kenya and CGHR. There were 18 participants present and seven presentations were made which focused on three main themes: (i) RSV disease burden in Kenya from existing data and planned studies, (ii) vaccine options, strategies for delivery and implementation and (iii) knowledge gaps. The data presented from studies in coastal Kenya, Nairobi and western Kenya, showed that burden of RSV disease is high among infants with incidence estimates of 10/100 with lower respiratory tract infection (LRTI), 6/100 with severe LRTI and 1-2/100 hospitalized in first year of life. RSV is a seasonal virus and its epidemic period varied across the different regions in Kenya. It was acknowledged that, data on the burden estimates in most parts of the country is still lacking. There is need for countrywide estimates that use standard methods including case definitions.

Currently scientists at CGHR and CDC-Kenya are taking an initiative to estimate the disease burden that will include data from different regions in Kenya.

It was also shown that there are over 40 RSV vaccine candidates in development, and 20 in clinical trials[1]. The leading candidate is a maternal boosting vaccine from Novavax which is a Nanoparticle F protein (post-fusion) subunit vaccine. This is for delivery to 3rd trimester pregnant women to boost infant antibody levels and protect them within the first 6 months of life when they are most at risk of severe RSV disease. In addition, a monoclonal high potency extended half-life prophylactic vaccine (pre-fusion) from Medimmune (Medi8897) designed for delivery to infants at birth and during RSV season is in Phase 2 trials. There are efforts by GAVI, PATH and WHO to make these vaccines affordable to low income countries. Programmatic issues associated with successful implementation of the maternal RSV vaccine including optimal gestational age for vaccine delivery during ANC visits, cultural or religious barriers for acceptance were discussed. A surveillance platform for influenza infection among pregnant women ongoing in Western Kenya will be utilized to assess baseline rates of adverse events during pregnancy and RSV disease burden among pregnant women.

During the round table discussion, it was agreed that more data is needed on patterns of RSV seasonality, incidence data finely stratified by age and population (in very young, elderly, pregnant women), data on life-threatening and fatal RSV, cost of illness data and cost-effectiveness studies of the strategy options and other strategies to address implementation issues for maternal RSV vaccine. As a way forward, plans for subsequent meetings and periodic updates will be circulated to all stakeholders once new data is available.

[1] PATH Snapshot (accessed 18/10/18) https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/

Introduction:

This meeting was an initiative of KEMRI-HJF, CDC-Kenya, and KEMRI-Welcome Trust who are collaborating on RSV work in Kenya. The group had identified a need to involve stakeholders countrywide to create awareness on RSV burden in Kenya within a global context of burden and vaccine development. This was relevant to planning possible future vaccine intervention and identifying knowledge gaps. See Appendix 1 for the invitation flier.

Meeting started at 10.30 am.

Participants:

Invitations were sent to 30 individuals who were representatives of the following organisations: KEMRI, CDC-Kenya, KEMRI-CGHR, KEMRI-Wellcome Trust Research Programme, FELTP, IDSRU, WHO-Kenya, KEPI, UNICEF, Kenya Pediatric Association, Pediatric group at KNH/UoN, Ministry of Health, National Vaccines Immunization Program, Kenya National Immunization Technical Advisory Group (KENITAG), Paediatric Infectious Disease Fellows/ Aga Khan University, National Influenza Centre and National Public Health Laboratories. Of these 22 participants confirmed attendance and 18 were present during the meeting. Full details are given in Appendix 2, with expanded acronyms.

Meeting Agenda/Discussion

1. A presentation for setting the scene: Highlighting the global burden of RSV disease, RSV Epidemiology, Vaccine Options and Knowledge gaps was given by Dr. Patrick Munywoki.

   Key Issues

   i. In the era of conjugate vaccines for *H.influenzae* and *S.pneumoniae*, RSV is the most important cause of early childhood severe LRTI globally
   ii. RSV is highly seasonal (periodic burden to health services), exists as two main groups A and B, multiple reinfections (immunity is not solid), disease severity declines rapidly with age resulting in very early age of disease (in particular the first 6months of life). Elderly also at risk.

iii. Vaccine pipeline healthy; front runner is a maternal boosting vaccine. Vaccination of early infants problematic hence various other strategies for delivery (increase passive RSV antibody to infant; reduce circulation in community; family cocoon vaccination; school children)

iv. Data on RSV in Kenya from a range of sources – in particular CDC-Kenya, KEMRI-CGHR and KEMRI-Wellcome Trust. These will be reviewed.

v. Gaps in knowledge exist – these will also be reviewed.

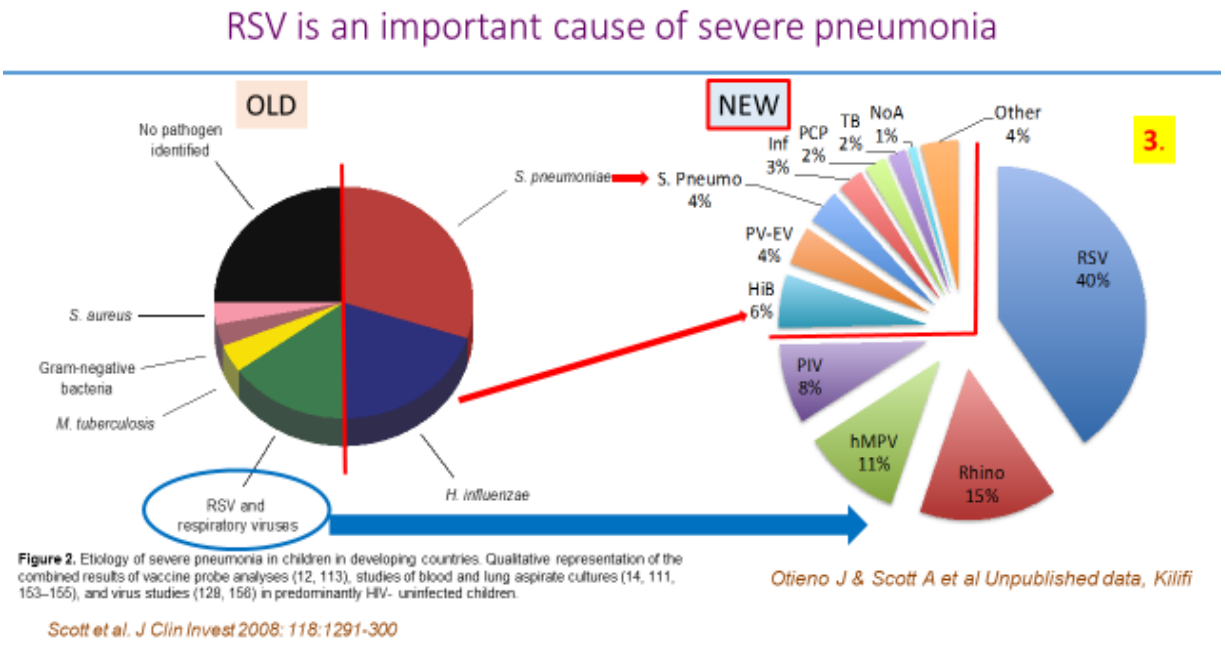


Figure 1: Pie Chart showing etiology of severe pneumonia in Children under 5 years in developing Countries. OLD and NEW signifies before and after the introduction of Hib and PCV vaccines respectively.

Questions/comments

i. Is there any explanation why RSV A is more common than RSV B?

ii. Is disease severity associated with RSV group?

iii. Is there any relationship between RSV and other co-morbidities such as malaria?
iv. RSV seasonal peaks observed in Kilifi have different timing to other parts of Kenya. Data from different geographical sites in the country are needed.

2. RSV Disease Burden in Kilifi: The long term RSV surveillance at Kilifi County Hospital and Data from Surveillance for Respiratory Diseases (SPReD) Studies in Africa, Kenya and Kilifi County was presented by Grieven Otieno

Key Issues

i. RSV disease surveillance has been going on since 2002. Including continuous surveillance of severe LRTI admissions of children than 5 years old to the county hospital; a birth cohort etc
ii. Data shows that burden of RSV disease is high among early infants, but also in later infancy and second year of life. Infant incidence estimates: 10/100 with LRTI, 6/100 with severe LRTI and 1-2/100 hospitalized in first year of life.
iii. A family cohort study revealed school-going children to be a major source of household RSV introduction leading to infant infection.
iv. Seasonality of RSV varies across different geographical regions in Kenya and in Africa.
v. Outpatient surveillance shows RSV ranked lower as a cause of ARI than for hospital patients but, nonetheless was at high prevalence among under 5 years.

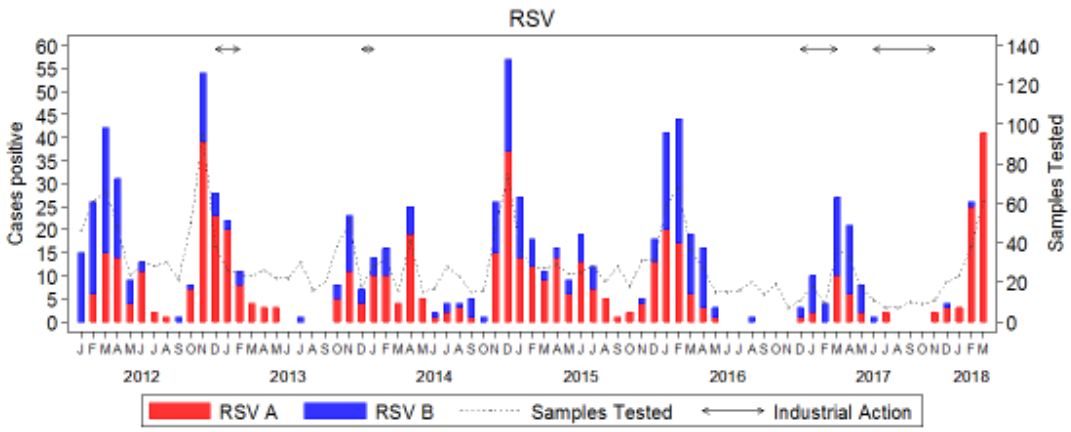


Figure 2: Seasonal Occurrence of RSVA and RSVB in Kilifi, Kenya: Data from Kilifi County Hospital Paediatric inpatient Surveillance 2012-2018.

Questions/comments

i. RSV seasonality is different across the country and in Africa region, what are the drivers for RSV seasonality?

ii. The burden of disease should capture all populations i.e. infants, pregnant women and the elderly, currently the data presented does not include all these groups.

iii. Does seasonality of RSV peak with other respiratory viruses?

iv. RSV is found not to be very common in older children from the schools SPRED study data, it is important therefore to find out where the young infants get RSV from.

3. Population Based Infectious Disease Surveillance (PBIDS) platform: Data on RSV disease burden-Lwak, Siaya and Kibera, Nairobi was presented by Dr. Godfrey Bigogo

Key Issues

i. Surveillance ongoing in Kibera, Nairobi and Lwak in Western Kenya.
ii. Participants given free care at study's referral clinics for all potentially infectious disease syndromes.
iii. Uses Severe Acute Respiratory Infection (SARI) and Influenza Like Illness (ILI) for case definition.
iv. Prevalence estimate given in the appended tables. Incidence estimates ….. these are needed

RSV-positivity results (March 2007-Feb 2011)

Age (yrs)	Sick visits	NP/OP Eligible n(%)	Swabs collected n(%)	RSV positive n(%)
Lwak				
<1	4938	1428 (28.9)	449 (31.4)	104 (23.2)
1-4	17325	4651(26.9)	1601 (34.4)	249 (15.6)
<5	22263	6079 (27.3)	2050 (33.7)	353 (17.2)
≥5	47019	4801 (10.2)	1962 (40.9)	148 (7.5)
Kibera				
<1	11512	1317 (11.4)	466 (35.4)	109 (23.4)
1-4	31705	3633 (11.5)	1150 (31.7)	170 (14.8)
<5	43217	4950 (11.5)	1616 (32.6)	279 (17.3)
≥5	48107	2431 (5.1)	1128 (46.4)	42 (3.7)

Questions/comments

i. Does the case definition used for surveillance (SARI/ILI) affect the estimation of disease burden? Consider revising the case definition.
ii. Should look at attributes of co-infections.
iii. Should also explore tracking the contact patterns at home and in school for children.
iv. Should look at potential residual smoke in relation to RSV.

4. Maternal Flu Cohorts: Western Kenya was presented by Nancy Otieno

Key Issues

i. Exposure to infections during pregnancy poses risk to both mother and baby.
ii. Data is scarce in Sub-Saharan Africa on pregnancy outcomes following disease infection.
iii. Bridging knowledge gap has value of maternal immunization strategies to protect infant.
iv. Platform involves a prospective cohort of pregnant women in Bondo and Siaya.
v. Women are followed up weekly till delivery with data and samples collected.
vi. The platform supports Influenza, RSV and other respiratory virus associated illness among pregnant women and their infants, including other studies such as GBS colonization, Zika virus infection, congenital CMV infection and metabolic gestational age assessment.

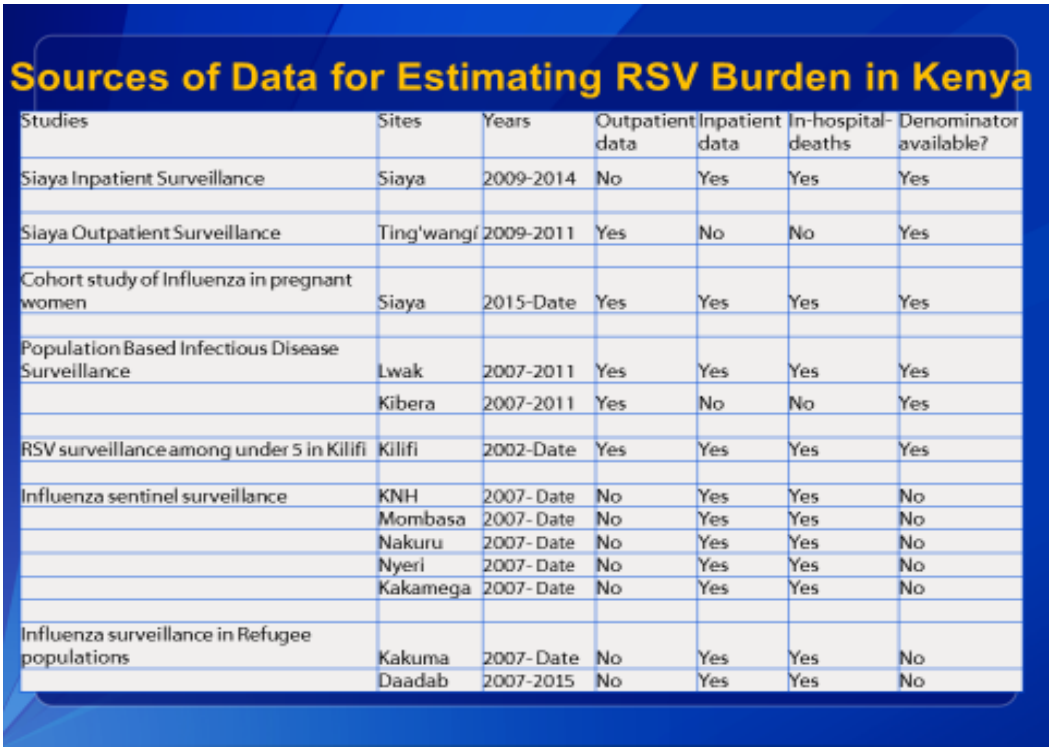
Cohort Enrollment, Follow-up and Delivery Updates, Jan, 2015–Sep, 2018

	N	%
MOTHERS		
Enrolled	2653	
Deliveries	2080	78.4
Hospital attended/home deliveries	2009/71	
Babies survived delivery	2015	96.9
Still births	53	2.5
Asphyxia	12	0.6
Maternal deaths	**4**	**0.2**
Miscarriages	29	1.1
Study withdrawals	73	2.1
Currently under follow-up	471	17.8
Gestational age at delivery (wk), median (range)	39	(19-45)
INFANTS		
Enrolled	2015	
Infant deaths	12	0.6
Study withdrawals/Loss to follow-up	9	0.4
Successful study completion	1646	81.7
Currently under follow-up	348	17.3

5. Estimating RSV disease burden in Kenya was presented by Bryan Nyawanda

   Key Issues

   i. Few studies have estimated RSV disease burden in sub-Saharan Africa.
   ii. In Kenya, RSV disease burden has been estimated in Coast and Western parts of the country only.
   iii. National burden of RSV still lacking.
   iv. This is important data to guide estimation of economic burden of RSV and cost effectiveness of vaccines.
   v. Plans under way to utilize data from different sites in Kenya to estimate RSV disease burden.
   vi. Approach is to estimate the base rates of SARI (Hospitalized and non-hospitalized) and then extrapolate to other regions.



Sources of Data for Estimating RSV Burden in Kenya

Studies	Sites	Years	Outpatient data	Inpatient data	In-hospital-deaths	Denominator available?
Siaya Inpatient Surveillance	Siaya	2009-2014	No	Yes	Yes	Yes
Siaya Outpatient Surveillance	Ting'wangí	2009-2011	Yes	No	No	Yes
Cohort study of Influenza in pregnant women	Siaya	2015-Date	Yes	Yes	Yes	Yes
Population Based Infectious Disease Surveillance	Lwak	2007-2011	Yes	Yes	Yes	Yes
	Kibera	2007-2011	Yes	No	No	Yes
RSV surveillance among under 5 in Kilifi	Kilifi	2002-Date	Yes	Yes	Yes	Yes
Influenza sentinel surveillance	KNH	2007- Date	No	Yes	Yes	No
	Mombasa	2007- Date	No	Yes	Yes	No
	Nakuru	2007- Date	No	Yes	Yes	No
	Nyeri	2007- Date	No	Yes	Yes	No
	Kakamega	2007- Date	No	Yes	Yes	No
Influenza surveillance in Refugee populations	Kakuma	2007- Date	No	Yes	Yes	No
	Daadab	2007-2015	No	Yes	Yes	No

Questions/comments

i. Requested for anyone interested in collaboration for estimating RSV disease burden to join the team to provide data for other parts of the country.
ii. The burden of disease estimation should also include data of circulating virus strains.
iii. Characterization of viruses be conducted by genetic sequencing.

6. RSV Vaccines and Strategy Options presented by Prof. James Nokes

Key Issues

i. Early Formalin Inactivated Vaccine (FIV) in the 1960s resulted in high proportion of trial participants experiencing enhanced disease following natural exposure.
ii. Vaccine pipeline healthy. 20 products in clinical phase trials. Major groups are (i) live attenuated, (ii) vectored, (iii) sub-unit/nanoparticle, (iv) passive immunoglobulin. Each have attributes for different target populations. One

vaccine (Novavax Nanoparticle) is in phase 3 trials for delivery to pregnant women to boost infant immunity in early months of life.

iii. A variety of delivery options in relation to age, serological status, catchment population, vaccine type.

iv. Live attenuated vaccines for infants have challenges of over / under-attenuation.

v. Front contender is the Novavax Nanoparticle F protein (post-fusion) subunit vaccine, delivered to 3rd trimester pregnant women to boost infant antibody levels.

vi. Strong contender also is the Medimmune high potency extended half-life passive antibody for delivery at birth or start of RSV season.

vii. Predictive models can play a part in exploring optimal strategy or strategy combinations.

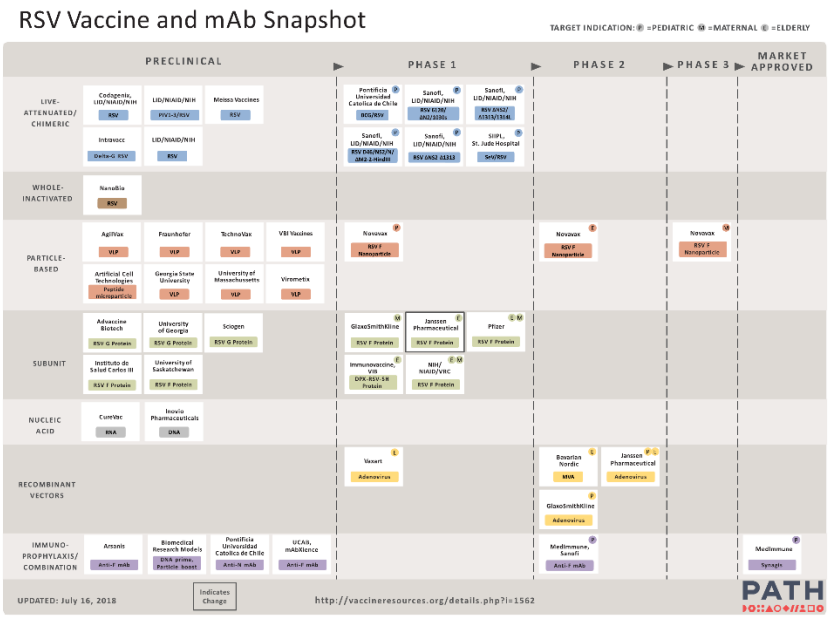


Figure 3: RSV vaccine and mAB snapshot by PATH accessed 18/10/2018

Questions/comments

i. Is Kilifi participating in clinical trials for the maternal RSV vaccine?

ii. What happens after the protective effect of the maternal vaccine?
iii. Is the type of RSV protective antibody the mothers develop known? Immune correlates not clearly understood.
iv. It will be important to map out the type and level of antibodies produced by the mother (pre- fusion or post fusion) to understand the antibodies that correlate with protection.
v. There are still concerns about the safety of vectored vaccines.

7. Issues of Implementation for a RSV maternal Boosting Vaccine was presented by Joyce Nyiro

Key Issues

i. There is some evidence that maternal antibodies protect against RSV disease.
ii. A maternal antibody boosting RSV vaccine is in phase 3 clinical trials in developed countries.
iii. There are efforts by GAVI, WHO, PATH to introduce and make the vaccine affordable to developing countries.
iv. There are still gaps to be addressed in Kenya for successful delivery and implementation of the maternal RSV vaccine. E. g, timing of ANC visits to inform of the optimal time for vaccine delivery with a high vaccine coverage, background rates of adverse events during pregnancy, rates of premature births, cost effectiveness data, barriers for vaccine uptake, stakeholder interest to support RSV maternal immunization policy.
v. Studies are planned to address these gaps.

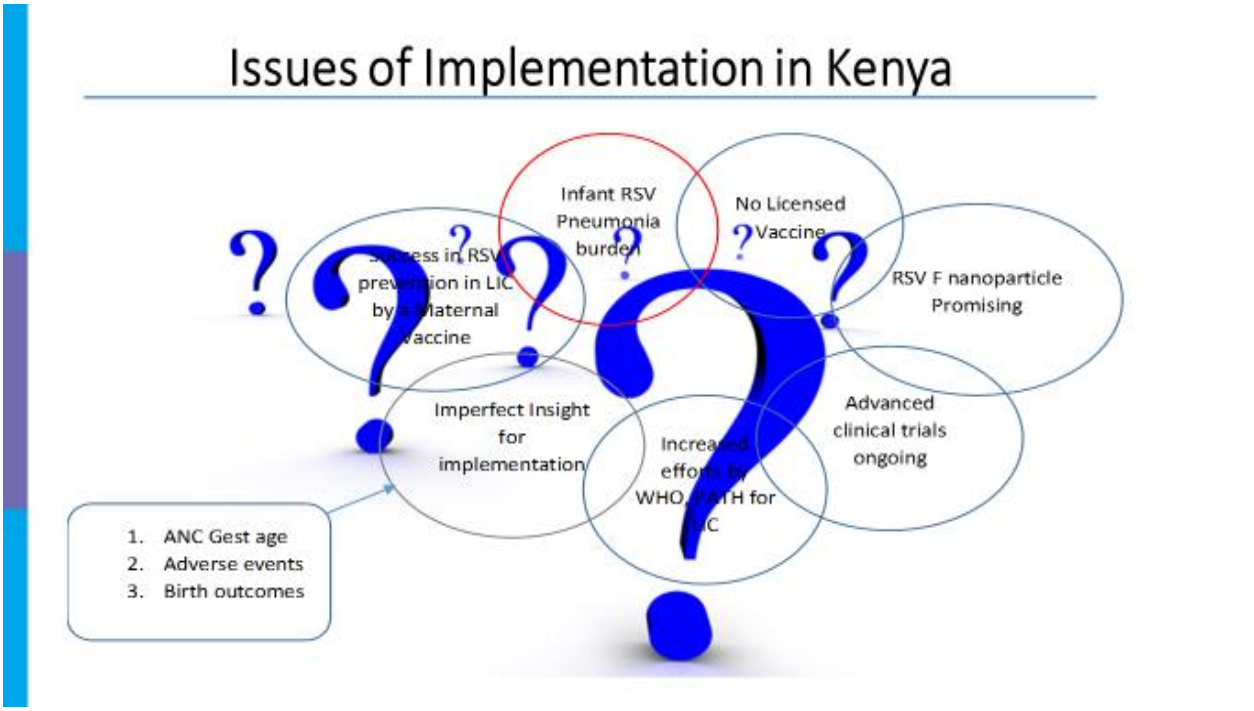


Figure 4: Schematic diagram highlighting the current issues likely to influence the implementation of RSV vaccines in Kenya

Questions/comments

i. When considering the optimum time for delivering a maternal RSV vaccine we should also understand priority is given to already existing vaccines and the optimum time should fit within those vaccination schedules.

ii. When planning about maternal immunization through ANC, we should take into account
   - Missed visits
   - Critical vaccination coverage
   - Visibility of protective of the infant.

iii. The information about RSV vaccination should be packaged in a way that will be easily understood by policy makers and arouse enough public health interest. I.e. How do we get on top of priority agenda and our community sees RSV disease as priority? Use an example of the HPV vaccine message packaging.

iv. Should conduct cost effectiveness studies to provide evidence for cost benefits of vaccine to policy makers.

8. Round Table Discussion Facilitated by Prof. James Nokes, Dr. Jennifer Verani and Prof. Wallace Bulimo.

Key Areas of Discussion

1. Priority areas to focus on in readiness for RSV vaccines?
   i. More data is required on RSV disease burden, mortality and baseline data on severe disease.
   ii. Incidence data from different geographical regions in the country and by finer age-groups.
   iii. Country mortality data as currently done by CHAMPS study in western Kenya
   iv. Knowledge of the different RSV genotypes circulating in the country.
   v. Data to show if the maternal vaccine will provide dual protection to both mother and the infant.

2. Vaccine trials for Kenya – what plans and what challenges?
   i. Maternal immunization not well taken up in Kenya, think ahead on what we can do about this with the community.

3. Thoughts regarding the timeline to licensed RSV vaccine for our setting?

4. Which strategies will be cost-effective, which feasible, for our setting?
   i. Current maternal vaccines would be made affordable for developing countries: efforts by PATH and GAVI.

5. Programmatic issues associated with vaccine delivery
   i. In case there is no data for clinical trials from Kenya, if data is available from countries with similar setting as Kenya can be used to guide policy.
   ii. Set up platforms for communication- Engage teams for communication in ministry of health e.g Infectious Disease Surveillance Response Unit. This will avoid challenges as experienced with second dose of measles vaccine.

iii. Package relevant public health messages to different stakeholders and use different platforms to sensitize the community e.g. Churches, Kenya Paediatric Association.

Meeting ended at 2.15 pm with a vote of thanks from Ms. Nancy Otieno

Appendix 1: Invitation Flier

Dear [],

Invitation - Stakeholders Technical Meeting on Respiratory Syncytial Virus (RSV), Kenya.

We are pleased to invite you to a half-day *'Stakeholder's technical meeting on RSV, Kenya'* to be held on **Monday**, **September 17th, 2018** at the **KEMRI HQ Conference Hall**, Nairobi, **10.00 – 1.00 PM**.

The meeting is an initiative of the KEMRI-Wellcome Trust Research Programme, CDC-Kenya and KEMRI-HJF, collaborating institutes involved in RSV studies in Kenya.

The collaboration has identified a need to update stakeholders on RSV burden and vaccine developments to inform early country-level discussion on strategies for RSV vaccine prospects intervention.

The context is a growing awareness of the major contribution of RSV to the global burden of infant and early childhood pneumonia and disease of the elderly, and significant steps forwards in vaccine development. In line with this there is increased interest in vaccine intervention from WHO and funding agencies, including BMGF, and GAVI the Vaccine Alliance, plans to recruit sites for maternal RSV vaccine candidate trials.

The workshop agenda focuses on scene-setting, RSV disease burden in Kenya (existing data and planned studies) and possible vaccine delivery strategies. There will also be a roundtable session on data gaps and cost-effectiveness analysis of potential strategies for Kenya.

Appendix 2: Participants' List

Stakeholders Present:

	Institution	Name	Email address	Telephone
1	WHO-KENYA /EPI/KEMRI HQ	Dr. Peter Borus	Pborus@kemri.org	0722793391
2	KEMRI HQ/EPI	Dr. Rosemary Nzunza	rnzunza@kemri.org	0724 886 446
3	KEMRI CDC/CGHR	Dr. Jennifer Verani	jverani@cdc.gov / qzr7@cdc.gov	0722721783
4	KEMRI CDC/CGHR	Dr. Sandra Chaves	bev8@cdc.gov	0710602748
5	KEMRI CDC/CGHR	Dr. Patrick Munywoki	pmunywoki@gmail.com /oha6@cdc.gov	0726676214
6	KEMRI CDC/CGHR	Dr. Godfrey Bigogo	GBigogo@kemricdc.org	0721517623
7	KEMRI CDC/CGHR	Ms. Nancy Otieno	Notieno@kemricdc.org	0720661245
8	KEMRI CDC/CGHR	Mr. Bryan Nyawanda	bnyawanda@kemricdc.org	0725765138
9	KEMRI-WT	Prof. James Nokes	JNokes@kemri-wellcome.org	0725514400
10	KEMRI-WT	Ms. Joyce Nyiro	JNyiro@kemri-wellcome.org	0722558143
11	KEMRI-WT	Mr. Grieven Otieno	GPOtieno@kemri-wellcome.org	0722401337
12	Kenya Pediatric Association / KENITAG	Dr. Evans Amukoye	amukoye@gmail.com	0722634383
13	Ministry of Health, National Vaccines Immunization Program	Dr. Collins Tabu	ctabu.epi@gmail.com / collinstabu@yahoo.com	0727771101
14	Paediatric Infectious Disease fellows/Aga Khan University Hospital /Kenya Paediatric Association	Dr. Adeel Shah	adeel.shah@aku.edu	0721485999

	Institution	Name	Email address	Telephone
15	National Influenza Centre (NIC)	Prof. Wallace Bulimo	wallace.bulimo@uonbi.ac.ke/ bulimow@gmail.com	0733616602
16	National Public Health Labs	Mrs. Mary Okeyo	Mokeyo53@gmail.com /Okeyomary@yahoo.com	0722472339
17	National Influenza Centre	Ms. Julia Wangui	Julia.wangui@usamru-k.org	0722615271
18	University of Nairobi/UNITID	Dr. Julius Oyugi	julias.oyugi9@gmail.com	0713898564

Stakeholders Absent with Apology:

	Institution	Name	Email address	Telephone
1	KEMRI CDC/CGHR	Dr. Marc-Alain Widdowson	zux5@cdc.gov	0702121124
2	IDSRU	Ms. Rosalia Kalani	rosaliakalani@yahoo.co.uk	0721535023
3	FELTP	Dr. Waqo Boru	wboru@feltp.or.ke / bbwaqo@yahoo.com	
4	Kenya Pediatric Association	Dr. Joe Mbuthia	jmbuthia@africaonline.co.ke	0720963887
5	Kenya Pediatric Association/Aga Khan Hospital	Dr. Adil Waris	dradilwaris@gmail.com	0733725972
6	Pediatric group at KNH/UoN	Dr. Irene Inwani	iinwani@yahoo.com	
7	Paediatric Infectious Disease fellows	Dr. Reena Shah	reena.shah@aku.edu	0711092789
8	Paediatric Infectious Disease fellows/KENITAG	Dr. Marybeth Maritim	mcmaritim@yahoo.com	0733729963

List of Abbreviations

KEMRI-Kenya Medical Research Institute

WHO-World Health Organisation

KEPI- Kenya Expanded programme on Immunisation

CDC-Center for Disease and Control

CGHR- Centre for Global Health Research

KEMRI-WT – KEMRI-Wellcome Trust Research Programme

KENITAG – Kenya National Immunization Technical Advisory Group

UNITID- University of Nairobi Institute of Tropical and Infectious Diseases

IDSRU –Infectious Disease Surveillance and Response Unit

FELTP- Field Epidemiology and Laboratory Training Program

KNH-Kenyatta Hospital

UoN- University of Nairobi

RSV - Respiratory Syncytial Virus

ARI- Acute Respiratory Infection

ILI- Influenza Like Illness

SARI- Severe Acute Respiratory Illness

Contact details for organizers

Prof. James Nokes
KEMRI-Wellcome Trust
Kilifi, Kenya
Tel: 0725514400
jnokes@kemri-wellcome.org

Prof. Sam Kariuki
Deputy Director Research and Development
KEMRI, Nairobi, Kenya
Tel: 0722232467
skariuki@kemri.org

Dr. Marc-Alain Widdowson
Centres for Disease Control (CDC-Kenya)
Nairobi, Kenya
Tel: 0702121124
(Widdowson) zux5@cdc.gov